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Targeting Tumor-Associated Macrophages by Anti-tumor Chinese Materia Medica*

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ABSTRACT Tumor-associated macrophages (TAMs) play a key role in all stages of tumorigenesis and tumor progression. TAMs secrete different kinds of cytokines, chemokines, and enzymes to affect the progression, metastasis, and resistance to therapy depending on their state of reprogramming. Therapeutic benefit in targeting TAMs suggests that macrophages are attractive targets for cancer treatment. Chinese materia medica (CMM) is an important approach for treating cancer in China and in the Asian region. According to the theory of Chinese medicine (CM) and its practice, some prescriptions of CM regulate the body's internal environment possibly including the remodeling the tumor microenvironment (TME). Here we briefly summarize the pivotal effects of TAMs in shaping the TME and promoting tumorigenesis, invasion, metastasis and immunosuppression. Furthermore, we illustrate the effects and mechanisms of CMM targeting TAMs in anti-tumor therapy. Finally, we reveal the CMM's dual-regulatory and multi-targeting functions on regulating TAMs, and hopefully, provide the theoretical basis for CMM clinical practice related to cancer therapy.

KEYWORDS tumor-associated macrophages, tumor microenvironment, Chinese materia medica, Chinese medicine, anti-tumor therapy

Infiltration of the tumor microenvironment (TME) by immune and inflammatory cells is involved in promoting tumorigenesis, tumor progression, local invasion and metastasis.[1] Tumor-associated macrophages (TAMs), a prominent and abundant inflammatory component of solid and hematological malignancies, express a pro- and anti-tumor effect in all stages of carcinogenesis. The molecular and functional phenotype of TAMs plays a key role in the tumorigenesis and progression.[2] A malignant tumor contains not merely proliferating neoplastic cells, but many other cells which constitute a microenvironment, for example, endothelial cells, fibroblasts, and infiltrating immune cells. TAMs, one of the important infiltrating immune cells, secrete an array of cytokines, chemokines, and enzymes that affect tumor progression, metastasis, and resistance to therapy.[3,4] TAMs secrete an array of cytokines, chemokines, and enzymes that affect tumor progression, metastasis, and resistance to therapy.[5-7] Clinical success in targeting macrophage (MΦ) in tumor patients suggests that TAMs might by attractive targets in combination therapy for tumor treatment.[8,9]

Chinese medicine (CM) is an important complementary medicine parallel to the conventional medicine system for tumor patients in China and other Asian countries. Chinese materia medica (CMM) is the natural therapeutic agent used under the guidance of CM theories.[10] CMM therapies are a long-term clinical practice, and share the characteristics of

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multi-component, multi-targeted and dual-regulatory function.[11] One of the mechanisms of CMM tumor therapy is related to regulating the internal environment and remodeling the TME, which coincides with conventional tumor therapy targeting the TME. CMM prescriptions, consisting of a single herb or combination of several herbs based on the theory of CM, have been used for treating and preventing various cancers during long-term popular practice or in combination therapy with chemotherapeutics.[7,12,13] The potential mechanism of anti-tumor effects of CMM includes increasing the efficacy of the therapeutic effect of chemotherapeutics including decreasing the development of chemoresistance or regulating the immune system.[14-16] It has been shown that CMMs have the effects of enhancing the immunological surveillance, regulating the body's internal milieu and remodeling the TME.[13]

In this article, we briefly introduce the origin, subpopulations, phenotypic characteristics and polarization of TAM and the TAM's effect on the TME in promoting tumorigenesis, metastasis, and immune suppression. Specifically we analyzed the effects and mechanisms of CMM prescriptions, extracts or active compounds on targeting TAMs in anti-tumor therapies. We also discuss the CMM's dual-regulatory and multi-targeting functions on regulating TAM, and hopefully, provide the theoretical basis for CMM use in clinical practice for cancer therapy.

Origin, Subpopulation and Polarization of TAM

MΦs involved in the immune responses appear to generate from circulating bone marrow monocytes, and are recruited to the TME by cytokines secreted by the tumor cells and other cells, then differentiated into various phenotypes and functions including anti- or pro-tumor activities.[5,17,18]

Subpopulations of MΦ

In *in vitro* models, MΦs have been classified as pro-inflammatory, classically activated MΦs (M1) and anti-inflammatory; alternatively activated MΦs (M2) based on their cell surface phenotypes and secreted cytokines.

M1-type MΦs, induced by Th1 mediators such as interferory (IFN)-γ, tumor necrosis foctor α (TNF-α) or lipopolysaccharides (LPS), release pro-inflammatory cytokines such as interleukin (IL)-12, IL-23. They express major histocompatibility complex (MHC) Ⅱ molecules, and have a high IL-12/IL-10 secretion ratio. M1 MΦs participate in the Th1 inflammatory responses primarily through production of pro-inflammatory mediators and up-regulation of cell surface molecules necessary for antigen presentation to activate Th1 cells and enhance the ability to phagocytose pathogenic material.[19,20] M2-type MΦs, typically induced by Th2 cytokines, mediate resistance to parasites, mediate immune regulation and tissue repair.[4,21] M2 MΦs release high levels of IL-10 and low levels of IL-12 and IL-23. In the context of cancer, however, M2 MΦs help driving tumor growth through the promotion of angiogenic programs, tissue remodeling, and directly or indirectly suppress cytotoxic T cell activity.[22]

The classification of MΦs in type M1 versus type M2 is an oversimplification of the *in vivo* situation. Most recently, Mosser and colleagues[23] suggested a new grouping of MΦ populations based on fundamental MΦ functions. This form of classification, though it may better reflect the heterogeneity and plasticity of MΦs in the TME, is clearly more difficult to consider and apply to research. The classical classification in M1/M2 MΦs is still commonly used as a valid and accepted concept for the sake of clarity.[2]

Polarization of MΦ

MΦs can be phenotypically polarized into diverse functional phenotypes by different microenvironment, and could have different effects during early or late tumor progression.[24] Tumor escape has been linked to a polarization switch from M1 to M2 MΦ phenotypes. In the early steps of tumor initiation, TAMs were mostly polarized towards a M1-like phenotype while during later steps of tumor progression they polarized mostly toward a M2-like phenotype.[24,25] In contrast, Wang, et al[26] reported a pro-metastatic role of M1-like TAM ($CD68^+$ $HLA\text{-}DR^+$) in hepatocellular carcinoma. This difference may be due to the different and complex environments of various cancers observed *in vivo*, which cannot yet be easily simulated *in vitro*. Many chemokines, such as C-X-C motif chemokine 12 (CXCL12),[27] and chemokine ligand 2 (CCL2),[28] signaling pathways, such as nuclear factor κB (NF-κB),[29] Notch receptors,[30] or hypoxia present in the TME[28] contribute to the polarization of TAM. The details of TAM function and CMM targeting MΦs will be presented below.

Effects of TAMs during Carcinogenesis and Anti-tumor Mechanisms of CMM Targeting TAMs

Many observations indicate that TAMs possess

M2-associated pro-tumor functions, including the induction of tumor angiogenesis and the stimulation of tumor cell proliferation, survival and invasion by producing inflammatory mediator, such as cytokines, and matrix metalloprotease (MMPs), or suppressing the cytotoxic effect of T cells.[2,31] TAMs play an important role in growth, metastasis and immunosuppression. Recently, studies showed that "TAM-specific therapies" may be a suitable option for further therapeutic approaches in cancer. Thus, CMM targeting TAMs may be considered as an additional anti-tumor therapy applicable to multiple stages of carcinogenesis.[19,32]

Tumor Initiation

It is now widely accepted that the nonmalignant cells of the TME evolve along with the growing tumor and provide essential cues supporting the modulation of TAM phenotype.[5] Chronic inflammation was shown to be associated with the development of malignant tumors by creating a tumor-promoting microenvironment.[33] MΦs are recruited to different areas of the TME and educated toward different phenotypes.[17,18] It has been shown that pancreatic cancer cells could activate MΦs *in vitro* to polarize toward an M2-phenotype, through the cytokines IL-4, IL-10 and CCL2.[34,35] This effect was confirmed by *in vivo* results revealing about 90% of all TAMs to be M2 MΦs. Accordingly, depletion of MΦs *in vivo* resulted in a significantly reduction in tumor growth.[36] Some Chinese herbal ingredients or prescriptions have been confirmed to effectively inhibit the recruitment and activation of MΦs to tumor sites and to re-educate TAM (see below).

Recruitment and Activation of TAMs

Diverse cytokines and polypeptides produced by tumor cells as well as microenvironment, such as hypoxia, are involved in guiding the recruitment, positioning and function of TAMs in the TME.[3] For example, CCL2, plays a pivotal role in many cancers, including pancreas, ovary, and breast in the recruitment and infiltration on MΦ into the TME.[34,35,37] In a pancreatic cancer mouse model, the inhibition of CCL2 was shown to reduce the recruitment of TAMs into the tumor, to improve the response to gemcitabine and increase the antitumor T-cell response and further inhibit tumor metastasis.[37,38]

CMM may regulate the recruitment and activation of MΦs in the TME by various pathways. Berberine, an isoquinoline alkaloid isolated from many medicinal herbs, such as *Coptis chinensis* Franch, inhibited the growth of CT26 tumor cells implanted subcutaneously in BABL/c mice and significantly reduced the density of $CD68^+/CD206^+$ TAMs. This is consistent with the notion that the anti-tumor effect of berberine involves inhibition of TAMs recruitment.[39,40] Epigallocatechin gallate (EGCG), a polyphenol present in green tea, inhibited tumor growth in a murine breast cancer model by inhibiting TAM infiltration and M2 MΦ polarization.[41,42] Praeruptorin D and E, the main constituents of *Peucedanum praeruptorum* Dunn, could protected BALB/c mice from lipopolysaccharide (LPS)-induced acute lung injury by inhibiting MΦs infiltration to the lung, cytokine release and vascular permeability.[43] Polysaccharopeptide (PSP), from *Coriolus versicolor* demonstrated anti-tumor and immune regulating effects.[44,45] PSP significantly increased the number of $CD14^+/CD16^+$ monocytes in phytohemagglutinin treated peripheral blood mononuclear cell model, but could not affect the proliferations of T-cells, natural killer, and B-cells. Thus, stimulating monocyte/MΦ with PSP could be an effective therapeutic intervention in targeting tumors.[46]

Astragalus polysaccharides (APS), the polysaccharide fraction of the roots of *Astragalus membranaceous*, were reported to activate MΦs in a toll-like receptor 4 (TLR4)-dependent manner while activating B cells via membrane Ig in a TLR4-independent manner.[45] Abrus agglutinin is a low-toxicity protein from the plant *Abrus precatorius* L. In its native (NA) and heat-denatured (HDA) forms, it activated TAMs in Dalton's lymphoma-bearing mice, and significantly increased *in vitro* cytotoxicity against tumor cells and stimulated production of nitric oxide but not of TNF-α. Thus, NA and HDA could be used as regulators of TAMs, for the treatment of cancer.[47] KSG-002, a 30% ethanolic extract of *Astragalus membranaceous* and *Angelica Sinensis* gigas at 3:1 w/w ratio, suppressed xenograft tumor growth and pulmonary metastasis via inhibiting TAM recruitment by blocking NF-κB-dependent TNF-α production.[48] Qinghao Biejia Decoction (青蒿鳖甲汤, QHBJ), a classical prescription consisting of *Artemisia apiacea*, turtle shell, *Rehmannia glutinosa* Libosch., *Anemarrhena asphodeloides* Bge. and *Paeonia suffruticosa* Andr, significantly reduced the incidence rate of dimethylbenzanthracene (DMBA)-induced ovarian cancer in rats, inhibited the infiltration of TAMs in ovarian tumors and down-regulated the expression of inflammatory mediators prostaglandin E_2 (PGE_2) and leukotriene B4 (LTB4) and the angiogenic

factor vascular endothelial growth factor (VEGF) in ovarian tumor tissues.[49] Shaoyao Decoction (芍药汤), a classical CMM prescription of *Paeonia lactiflora* Pall effective in treating ulcerative colitis, could significantly increase the survival of mice with azoxymethane (AOM)/dextran sodium sulfate (DSS)-induced colitis-associated colorectal cancer (CA-CRC) by reducing the infiltration of TAM and thereby decreasing the expression levels of serum IL-1β, IL-6, and TNF-α.[48] PHY906 (KD018), a CMM prescription consisting of *Glycyrrhiza uralensis* Fisch, *Paeonia lactiflora* Pall, *Scutellaria baicalensis* Georgi, and *Ziziphus jujuba* Mill, may potentiate sorafenib action by up-regulating the expression of CCL2, which could attract M1-type MΦs and exert an anti-tumor activity.[49]

Re-programing of TAM Phenotype

Mantovani proposed that TAM exert pleiotropic functions that can influence tumor growth and progression in opposite directions.[35] Recently, researches confirmed that circulating monocytes were recruited to the TME by chemotactic factors produced by tumor cells and differentiated toward the M2 phenotype.[52-54] M2 MΦs release various growth factors and cytokines to promote tumor cell invasion, induce angiogenesis, suppress antitumor immunity, and accelerate tumor cell metastasis.[55,56] The polarization of TAM was a regulated and reversible process and dependent on the TME. It was shown that a predominance activation of NF-κB and signal transducers and activators of transcription (STAT) 1 promoted M1 MΦ polarization resulting in cytotoxic and inflammatory activities, while STAT3 and STAT6 activation resulted in M2 MΦ polarization leading to immune suppression and tumor progression.[57,58]

CMM targeting TAMs could act as an anti-tumor prescription by aiming at preventing polarization of TAMs toward a more anti-tumor phenotype. Emodin, a natural anthraquinone derivative isolated from *Rheum palmatum* L., inhibited MΦ recruitment and M2 polarization by suppressing STAT6 phosphorylation and C/EBPB expression in the 4T1 and EO771 orthotopic breast cancer mouse models.[59,60] Isoliquiritigenin (ISL), a flavonoid from *Glycyrrhiza uralensis* Fisch, inhibited M2 MΦ polarization by down-regulating PGE_2 and IL-6-mediated signaling in a mouse model of AOM/DSS-induced colitis-associated tumorigenesis. In parallel, ISL also blunted the M2 polarization of RAW264.7 cells and mouse peritoneal MΦs by inactivating PGE_2/peroxisome proliferator-activated receptor δ and IL-6/STAT3 signaling *in vitro*.[61] Sinomenine, an alkaloid extracted from *Sinomenium Acutum*, has been used to treat rheumatism in China. Zhang, et al[62] found that treating breast cancer-bearing mice with 100 mg/kg sinomenine hydrochloride (SH) can provide a self-reinforcing stimulus for further polarizing TAMs away from an M2-like phenotype toward an M1-like phenotype thereby contributing to its anti-tumor and anti-metastasis effect. The aqueous extract of *Crinum latifolium* L. leaf induced expression of TNF-α, IL-1β and IL-6 and promoted MΦs differentiation into the pro-inflammatory M1 phenotype.[63] The *Sarcandra glabra* polysaccharide (SGP) could effectively increase expression of CD14, CD16/32 and CD40 in MΦs induced by IFN-γ, which indicated the potential for applications in regulating the immune balance in the treatment of cancer.[64] Fuzheng Jiedu Decoction (扶正解毒汤, FZJD), a prescription consisting of *Astragalus membranaceous*, *Codonopsis pilosula*, *Atractylodes macrocephala*, *Lycium barbarum*, *Smilax glabra*, *Polygonum multiflorum*, and *Actinidia arguta*, reduced the expression of the M2 MΦs specific genes Arg-1 (an immunosuppressive enzyme) and CCL22 (a chemotactic chemokine) in an *in vitro* co-culture system of RAW264.7 MΦs and mesenchymal stem cells.[13] FZJD combined with 5-fluorouracil (5-FU) inhibited the marker of M2 MΦs subtype expression and increased the marker of M1 MΦs subtype expression, resulting in the inhibition of tumor recurrence and metastasis in a gastric cancer model.[65]

In some excessive inflammatory reactions, active CMM components could promote phenotype transition from M1 to M2, thus acting as anti-inflammation drug. Berberine down-regulated the content of TNF-α and the mRNA expression levels of inducible nitric noxide synthase (iNOS) and suppressor of cytokin signaling (SOCS) 3 in MΦs induced by LPS, inhibited the content of IL-10 and the mRNA expression level of Arg-1 in MΦs induced by IL-4, but did not modify SOCS2. The results indicate that berberine has an effect on inhibiting the M1 and M2 polarization of MΦs *in vitro* and may play a regulatory role in the dynamic balance of M1/M2 phenotype.[66] The similar results were found in many compounds or CM prescription, such as curcumin,[67] arctigenin,[68] and Xuebijing Injection (血必净注射液).[52]

Importantly, CMM can act in a dual-regulatory function in the inflammatory reaction depending on the

specific physiological or pathological processes and the tissues involved. CMM can suppress excessive inflammation, while promoting the polarization of anti-inflammatory M2 MΦs into M1 phenotype thereby altering the state of immuno-suppression in the TME of advanced cancers.

Tumor Metastasis

The process of metastasis represents a critical phase in the neoplastic cascade, and growing evidence indicate a tight link between metastasis and TAMs, whereby TAMs produce inflammatory cytokines, stimulate the growth of tumor cells and promote tumor cell migration and metastasis. TAMs contribute to tumor progression also by producing several factors enhancing angiogenesis and lymphogenesis.[34,69]

TAMs have been reported to promote angiogenesis via the production of diverse pro-angiogenic factors such as transforming growth factor-β (TGF-β), VEGF, Platelet derived growth factor (PDGF), fibroblast growth factor (FGF) and angiogenic chemokines, such as CXCL12.[70,71] They also regulate matrix degradation through the production of matrix-degrading enzymes such as MMPs, plasmin, and urokinase-type plasminogen activator (uPA).[69,72] Clinical research has confirmed that M2-polarized TAMs are associated with poor prognoses in several cancers, including classical Hodgkin's lymphoma (CHL),[73] lung adenocarcinoma,[74] and pancreatic cancer.[75] Ding, et al[76] found a significant correlation between the expression of CD68 or CD163 protein with a tumor size, lymph node metastasis, and vascular invasion in patients with pancreatic cancer consistent with the role of TAM infiltration in pancreas and the promotion of pancreatic cancer development.

Angiogenesis and Lymphangiogenesis

Angiogenesis and lymphangiogenesis are critical processes for tumor growth, invasion, and metastasis. TAMs promote angiogenesis in a wide type of tumors, such as gliomas, carcinomas of the esophagus, breast, bladder, and prostate by releasing vascular growth factors (mainly VEGF and PDGF), cytokines (e.g. TGF-β), proteases, and chemokines.[77] TAMs support tumor lymphangiogenesis not only by secreting pro-lymphangiogenic factors, such as VEGF-A and MMP-9, but also by trans-differentiation into lymphatic endothelial cells.[78] Wogonin, a flavonoid isolated from the root of *Scutellaria baicalensis*, inhibited tumor growth, metastasis, angiogenesis and lymphangiogenesis, and reduced the number of TAM in the tumors of LM8-bearing mice. Wogonin inhibited VEGF-C-induced lymphangiogenesis through the reduction of VEGF-C-induced VEGF receptor-3 phosphorylation.[79] Recently a phenolic alkaloids of *Menispermum dauricum* (PAMD) inhibited BXPC-3 tumor growth and angiogenesis by reducing the production of VEGF, and basic fibroblast growth factor (bFGF).[80] Many results show that genistein, a soy isoflavonoid, inhibited angiogenesis through the regulation of VEGF, MMPs, and epidermal growth factor receptor expressions, thereby resulting in a strong anti-tumor effect.[81,82] Qingyi Huaji Decoction (清胰化积汤, QYHJ), consists of many herbs including the radics of *Paeonia lactiflora* Pall and *Scutellaria baicalensis* Georgi, has been used as an integrative agent in the clinical treatment of advanced pancreatic cancers, especially those with liver metastasis. QYHJ inhibited the growth of human pancreatic cancer cell line CFPAC-1 *in vivo*, and this correlated with the down-regulation of serum level of pro-angiogenic factors sVCAM-I, TNF-α, bFGF, IL-6 and IL-8.[83] Besides, QYHJ exerted an inhibitory effect on the growth of experimental liver metastasis in nude mice inoculated intra-splenically with the human pancreatic cancer cell line SW1990, in part though the inhibition of VEGF and Cyr61 expression.[84] QYHJ inhibited cancer-related inflammation in the SW1990HM (pancreatic tumor cell line with high metastasis) tumor model by decreasing infiltration of TAM and IL-6 production and resulting in the decreased epithelial-to-mesenchymal transition and cell invasion.[85] Hongjingtian Injection (红景天注射液), a CMM standardized Tibetan herbal product extracted from *Rhodiola crenulata* L., used to treat patients with acute ischemic stroke or coronary heart disease, inhibited the metastasis of human non-small cell lung cancer by reducing the production of VEGF.[86]

Matrix Remodeling

In the tumor stroma, MΦs can produce enzymes promoting matrix degradation, such as MMPs, uPA and uPA receptor, and plasmin, thereby facilitating invasion and metastasis of tumor cell.[34] Emodin exerts anti-proliferative and anti-metastatic activity in pancreatic cancer both *in vitro* and *in vivo*, which may be related to the down-regulation of NF-κB and its regulated molecules survivin and MMP-9.[87] Gallic acid and gallic acid dimmer, polyphenols extracted

from pericarp of water caltrop, significantly decreased MMP-9 activity and inhibited migration of gastric cancer cells; TNF-α and IL-6 associated with migration and angiogenesis were also significantly reduced.[88] Aloe emodin, an anthraquinone from *Rheum palmatum* L., has anti-migratory and anti-angiogenic activities in colon cancer cells by down-regulating expression of MMP-2/9, RhoB and VEGF.[89] Honokiol, a major phenolic compound isolated from the root and stem bark of magnolia, inhibited the expression of MMP-9 in PANC-1 cells *in vitro* and VEGF in tumor tissue *in vivo* in an athymic mouse tumor model.[90]

Immune Suppression

TAMs also produce various immune suppressive factors, including PGE_2, indoleamine 2,3-dioxygenase, Arg-1, and IL-10 to suppress tumor-associated antigen-specific T cell immunity and thus contribute to immunosuppression.[31,34] The major immune stimulatory cytokine IL-12 may be due to the activity of IL-10, produced either by TAM or by the tumor cells. Part of the immune suppressive activity of TAM is exerted indirectly by their release of chemokines, such as CCL18 and CCL22 that preferentially attract T cell subsets devoided of cytotoxic functions.[91] These immune stimulatory cytokines and chemokines could be the potential targets of anti-tumor CMM. Different reports indicate that polysaccharides from CMM herbs could improve the amount of MΦs in the TME, enhance phagocytosis, as well as stimulate the secretion of NO, TNF-α, IL-1, etc., possibly related with M1 MΦs activation and polarization.[92]

Direct Effect on MΦs

PAC-I, a mannose-rich polysaccharide fraction from *Aloe vera* L. var. chinensis (Haw) Berg., increased the expression of MHC-Ⅱ and FcγR, and enhanced endocytosis, phagocytosis, NO production, TNF-α secretion and tumor cell cytotoxicity *in vitro*, stimulated systemic TNF-α production *in vivo* and prolonged the survival of tumor-bearing mice. The results may have therapeutic implications of PAC-I in tumor immunotherapy.[93]

Regulation of Immune System

Salidroside, an active component of *Rhodiola rosea* L., promoted proliferation and phagocytosis of peritoneal MΦs stimulated by LPS and IFNγ, and reduced the production of reactive oxygen species, but promoted the production of NO, and in activated peritoneal MΦs.[94] Li, et al[95] demonstrated that berberine inhibited the proliferation of Ishikawa endometrial carcinoma cancer cells co-cultured with TAM and the production of IL-8, while blocking NF-κB signaling pathway to restrain metastasis formation. Cucurbitacin D, an oxygenated tetracyclic triterpenoid isolated from *Trichosanthes kirilowii*, increased LPS-induced IL-1β production in culture supernatant of MΦs, indicating that cucurbitacin D could initiate immune regulating activity in MΦs and possibly function as anti-tumor drug.[96] 20S-dihydroprotopanaxadiol, a protopanaxadiol derivative found in *Panax ginseng* exhibiting various biological activities including anti-cancer, pro-apototic, and anti-inflammatory effects, boosted innate immune responses of monocytes and MΦs.[97] Garlic lectin was shown to induce IL-12 production via activation of p38 MAPK/ERK in mouse MΦs and to stimulate IFN-γ production in spleen cells, consistent with anti-tumor effects.[98] Many studies showed that polysaccharides could enhanced cytotoxic and phagocytic activities of immune cells and increased the productions of many Th1 cytokines via various signaling pathways, such as *Panax ginseng* Polysaccharide,[99] *B. striata* Polysaccharide,[100,101] Polyporus polysaccharide,[102,103] *Plantago asiatica* L. Polysaccharide,[104] *Ganoderma lucidum* Polysaccharide.[105] These effects induced anti-cancer effect indirectly though the activation of immune cells rather than via direct cytotoxic effects.[106,107] Water-soluble polysaccharide extracted from *Sanguisorba officinalis* L., significantly inhibited the growth of mouse transplanted tumor, remarkably increased the spleen index and promoted splenocytes proliferation, MΦ phagocytosis and secretion of serum cytokines IL-2, TNF-α and IFN-γ in sarcoma 180-bearing mice in the absence of direct cytotoxic activity on tumor cells. These results indicated that the anti-tumor activity of SOP may be achieved through immune potentiation.[108] These results were confirmed by other researchers using different CMM, such as polysaccharide from *Limonium sinense* Kuntez,[109] *Lilium* sp.,[110] *G. lucidum*[111] and Weikangfu Granule (胃康复胶囊), a drug preparation used to treate gastric cancer and consisting of *Curcuma wenyujin*, *Astralagus membranaceous*, *Glycyrrhiza inflate*, *Poria coco*,[112] and Shenqi Fuzheng Injection (参芪扶正注射液), a CMM standardized product extracted from radices *Codonopsis* sp. and *Astragali* sp. to improve immune function against chronic diseases.[113] PSSC, polysaccharides from *Salvia chinensis* Benth, suppressed growth of H22 cells and reduced serum levels of PGE_2 in mice, suggesting an anti-tumor immune-stimulatory

activity.[114] Two basidiomycete species, *Lentinus edodes* and *Cordyceps sinensis*, increased IL-2 production in LBRM-33 1A5 T cells, through indirect action on MΦs, without directly acting on T cell.[115] Qingshu Yiqi Decoction (清暑益气汤), a CMM prescription consisting of nine herbs including *Astragalus membranaeus*, *Panax ginseng* and *Sculellaria baicalensis*, has been classically used for treating fever and pulmonary disorders. Tumor burden and losses of muscle mass were found to be significantly decreased when 5-FU was combined with this Chinese prescription, suggesting that the combination of *S. baicalensis* and QYD is able to ameliorate cachectic symptoms and positively stimulate anti-tumor immunity in mice undergoing chemotherapy.[116]

Conclusion

CM, respectively CMM, belongs to a natural medicine system, which is still in active practice as an alternative therapeutic possibility beyond the origin cultural region. Based on this medicine system, many new medications have been developed, such as compounds isolated from *Artemisia annua*, and minnelide (a potential anti-pancreatic cancer medication, modified from triptolide).[117-119]

In the last two decades, experimental and clinical evidence showed that most chronic diseases, including cancer, are caused by a dysregulated inflammatory-immune response, and TAMs are a key link between inflammation and cancer in regulating tumor growth, progression and response to anticancer drugs.[120] CMM demonstrated obvious anti-tumor effects based on its characteristics of multi-components and multi-targets. The anti-cancer properties of CMM targeting TAMs were shown to involve the following mechanisms: (1) inhibition of the production of cytokines or chemokines associated with TAM recruitment and activation; (2) promotion of MΦs phenotype conversion from M2 to M1; (3) reduction of the production of pro-tumoral cytokines secreted by TAM including angiogenic and lymphangiogenic factors;[78] (4) reshaping of the TME to inhibit the immunosuppressive responses.

Most findings of anti-tumor CMM targeting MΦs or immune regulation are related to the expression level of cytokines or chemokines in the TME. More investigations are required, however, to unravel the mechanism involved and identify active components of CMM prescriptions. CMM prescriptions are highly complex systems, and interactions between different components commonly exist.[121] For example in the case of extracts of radices *Astragalus membranaceous* and *Angelica sinensis* in different proportions (e.g. w/w ratio) opposite effects related to cancer pulmonary metastasis were observed and should be investigated.[48]

In this article, we have analyzed the literature for studies focused on cancer therapy related to CM and CMM. It is not just limited to active single substances, classical prescriptions, but it also includes combinations with conventional therapies, and the putative targeting phase in cancer development as listed in Figure 1. Further investigations are required to better characterize the anti-tumor effects of CM and CMM. In order to develop novel anti-tumor therapies based on CMM it will be essential to confirm results obtained in *in vitro* studies addressing molecular mechanisms of action on TAMs by performing *in vivo* studies on tumor progress.[122]

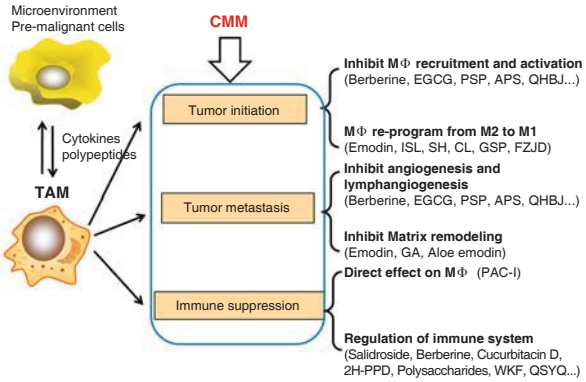

Figure 1. Anti-tumor CMMs Targeting TAMs Effects on Tumor Progression

Notes: Pre-malignant or malignant cells and microenvironments, such as inflammation or hypoxia, generated various cytokines, chemokines, and enzymes to recruit and activate macrophages. The TAMs, interacted with TME and other cells, re-programmed into diverse functional phenotypes to affect tumor initiation, metastasis, and immune suppression. Anti-tumor CMM compounds or prescriptions targeting TAMs could effect on different phases of tumor growth through different mechanism.

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